DOI: 10.1002/adsc.201500768

Rhodium(III)-Catalyzed Synthesis of Aryl Spirocycles by Aromatic C–H Activation/Intramolecular Heck-Type Reaction

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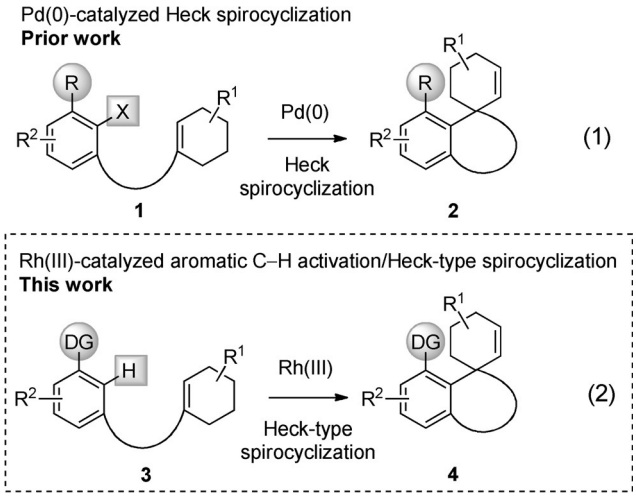
Received: August 16, 2015; Revised: September 15, 2015; Published online: November 25, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500768.

Abstract: The rhodium(III)-catalyzed aromatic C–H activation/intramolecular Heck-type reaction has been studied to synthesize spirocyclic compounds, an important class of molecules in medicinal chemistry and natural product synthesis. This approach was efficient with a variety of substituted *N*-methoxybenzamides tethered to different cyclic alkenes having a 5-, 6- or 7-membered ring. This practical method affords sterically hindered *o*-substituted aryl spirocycles that are valuable compounds for further functionalization to access relevant building blocks.

Keywords: catalysis; C–H activation; Heck-type reaction; rhodium; spiro compounds



Scheme 1. Intramolecular Heck spirocyclization catalyzed by Pd(0) *vs.* Rh(III).

The spirocyclic scaffold is a unique structural feature commonly embedded in various natural products and synthetic congeners that possess a wide spectrum of biological properties.[1] Spiro-linked heterocycles have been incorporated in numerous classes of pharmaceutically active molecules and are considered by medicinal chemists as "privileged structures" in drug discovery.[2] The importance of spirocycles has also been illustrated by their use as valuable synthetic intermediates in the total synthesis of natural products. Despite the utility of spirocyclic compounds, the efficient formation of the spiranic quaternary carbon is still an important challenge in organic synthesis.

Intramolecular Heck arylation reactions catalyzed by Pd(0) are useful methods to build spirocycles **2** embedding an aryl moiety [Scheme 1, Eq. (1)], which have been used in several total syntheses of natural products.[3] However, in this approach the introduction of the halogen atom can be a long and tedious process, especially for substrates bearing an *ortho*-substituent (**1**, R ≠ H).

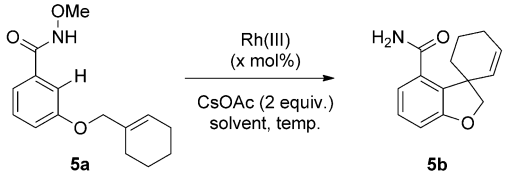
Recently, the metal-catalyzed aromatic C–H (ArC–H) activation reaction directed by a neighbouring group has received tremendous interest.[4,5] Because of its high efficiency, functional-group tolerance and selectivity, rhodium(III) catalysis has emerged, over the last few years, as a powerful tool in ArC–H activation.[5] Among the numerous transformations catalyzed by Rh(III), the oxidative Heck-type olefination has been extensively studied. This has resulted in the development of several intermolecular reactions directed by different functional groups such as amides,[6] protected anilines,[7] ketones,[7] ArCONH–OMe,[8] $ArNR_2$–O,[9] etc. Recently, it has been showed that benzamides (ArCONH–R) are able to direct the rhodium(III)-catalyzed intramolecular reaction with a tethered olefin. Depending on the nature of the amide, a hydroarylation (R = Me), amidoarylation (R = OPiv) or Heck-type reaction (R = OMe) can be performed.[10] However, the studies has been limited to the synthesis of functionalized fused heterocycles.

Our interest in the synthesis of aryl spirocyclic compounds,[4a,d] led us to investigate the Rh(III)-catalyzed Heck-type spirocyclization of aryl alkenes **3** [Scheme 1, Eq. (2)].[11]

We describe herein the successful development of a practical, regioselective and efficient synthesis of highly hindered *o*-substituted spirocycle **4** from easily accessible cyclic alkene **3**. Moreover, we demonstrate that compound **4** can be used as a platform to access a variety of densely functionalized spirocycles.

Investigations were first carried out by selecting alkene benzamide **5a** and subjecting it to a catalytic amount of $[RhCp^*Cl_2]_2$ with 2 equivalents of CsOAc in methanol ($c = 0.2$ M) at room temperature (Table 1). Under these initial conditions, we observed a clean reaction, which afforded exclusively the desired spirocycle **5b** isolated in 71% yield after 12 h (entry 1). This result contrasts with the recent report from Rovis et al. that showed on one example that the benzoate-directed Heck-type reaction with a tethered cyclohexene performs in moderate yield (54%) and also gave 20% of impurity.[10c] Increasing the temperature to 60 °C significantly decreases the reaction time to 2 h to afford **5b** still in good isolated chemical yield (entry 2). The use of a silver additive ($AgSbF_6$ 20 mol%, entry 3) or other rhodium catalyst {$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$, entry 4} did not have a significant influence on the yield. Among the different solvents tested (*t*-AmOH, 1,2-DCE or CH_3CN, entries 5–7), we found that *tert*-amyl alcohol provided the spirocycle **5b** with the highest isolated yield (86%, entry 5).

Table 1. Optimization of the Rh(III)-catalyzed Heck-type spirocyclization of **5a**.



5a **5b**

Entry	Catalyst (mol%)	Solvent	*T* [°C]	*t* [h]	Yield [%][a]
1	$[RhCp^*Cl_2]_2$ (2.5)	MeOH	25	12	71
2	$[RhCp^*Cl_2]_2$ (2.5)	MeOH	60	2	73
3[b]	$[RhCp^*Cl_2]_2$ (2.5)	MeOH	60	2	71
4	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5)	MeOH	60	2	73
5	$[RhCp^*Cl_2]_2$ (2.5)	*t*-AmOH	60	2	86
6	$[RhCp^*Cl_2]_2$ (2.5)	1,2-DCE	60	2	28[c]
7	$[RhCp^*Cl_2]_2$ (2.5)	MeCN	60	2	71

[a] Isolated yield.
[b] 10 mol% of $AgSbF_6$ was used.
[c] Conversion estimated by ^{1}H NMR on the crude mixture.

The optimized conditions of the Rh(III)-catalyzed Heck-type spirocyclization were then applied to a variety of substituted benzamides tethered to a cyclic alkene by different linkers (Table 2). We observed in most cases that the substitution of the aryl moiety decreased the reaction rate. Thus, unless otherwise mentioned, we carried out all the reactions at 60 °C overnight. Gratifyingly, we found that the substitution on the aryl moiety was well tolerated to afford [6,5,6]-spirocycles (entries 1–6). For instance, the *ortho*-fluoro-substituted benzamide **6a** cyclized into the tricyclic compound **6b** in 88% (entry 1). Other substrates **7a** and **8a** bearing an *ortho* electron-withdrawing (NO_2, entry 2) or electron-donating (OMe, entry 3) group respectively reacted well to provide **7b** and **8b** in good yields.

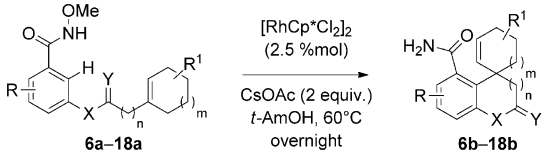
Electron-rich benzamides **9a** bearing a dioxolane (entry 4), and **10a** tethered to two cyclic alkenes (entry 5) gave products **9b** and **10b** in 70% and 83% yields, respectively. The steric hindrance around the amide moiety (i.e., **11a**, entry 6) did not affect the reactivity, since **11b** was isolated in 76% yield. In contrast, cyclization of the sterically demanding cyclohexene **12a** derived from myrtenol, took place at 100 °C over 3 days to afford the spirocycle **12b** in 60% yield (69% brsm, entry 7).

We next investigated the effect of the ring size of the cyclic alkene with substrates **13a** and **14a** (entries 8 and 9). Under the optimal reaction conditions they afforded the corresponding [6,5,5]- and [6,5,7]-spirocycles **13b** and **14b**, respectively, in good yields. Furthermore the [6,6,6]-tricyclic compound **15b** could be obtained with a 73% yield by cyclization of **15a** (entry 10).

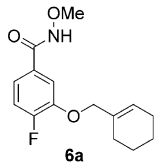
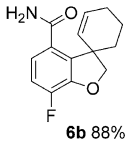
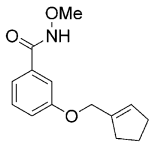
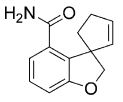
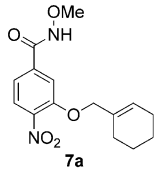
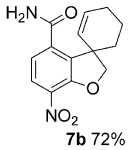
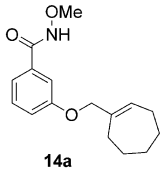
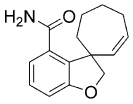
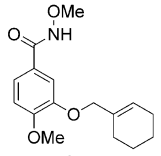
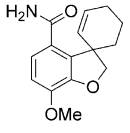
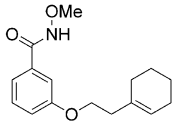
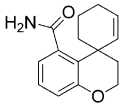
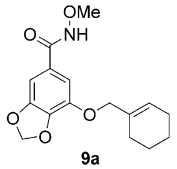
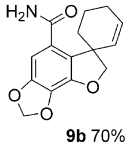
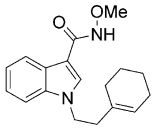
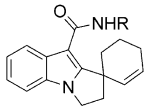
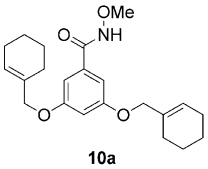
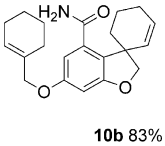
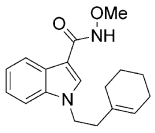
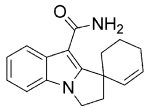
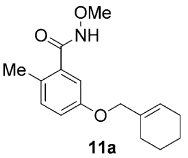
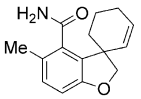
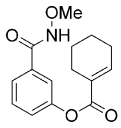
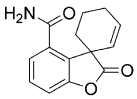
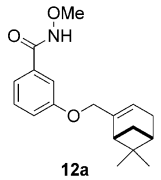
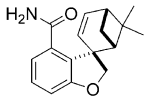
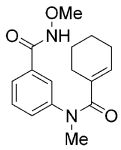
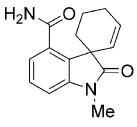
Substrates bearing a different linker between the benzamide and the cyclic alkene were then examined. For instance, the indole derivative **16a** was subjected to the optimal catalytic system at 80 °C. With this substrate, the cyclization was found to be sluggish, and only 50% of the starting material was consumed after 3 days (entry 11). However, we were able to isolate the desired product **16b** in 23% yield as well as 10% of the cyclized NHOMe amide **16c** (R = OMe). This result indicates that the rhodium(I) species generated after the reaction is not efficiently reoxidized into Rh(III). Gratifyingly, the use of $Cu(OAc)_2$ (2.1 equiv.) as an external oxidant in combination with $AgSbF_6$ (10 mol%) afforded the indole derivative **16b** in an improved 57% yield (entry 12).[12]

Spirobenzofuran-2-one and spirooxindole units are important structural motifs found in natural and unnatural compounds with diverse and important biological activities.[13] We showed that using this methodology we were able to cyclize the ester linked benzamide **17a**, to give spirobenzofuran-2-one **17b** in 77% yield (entry 13). Furthermore, the reaction per-

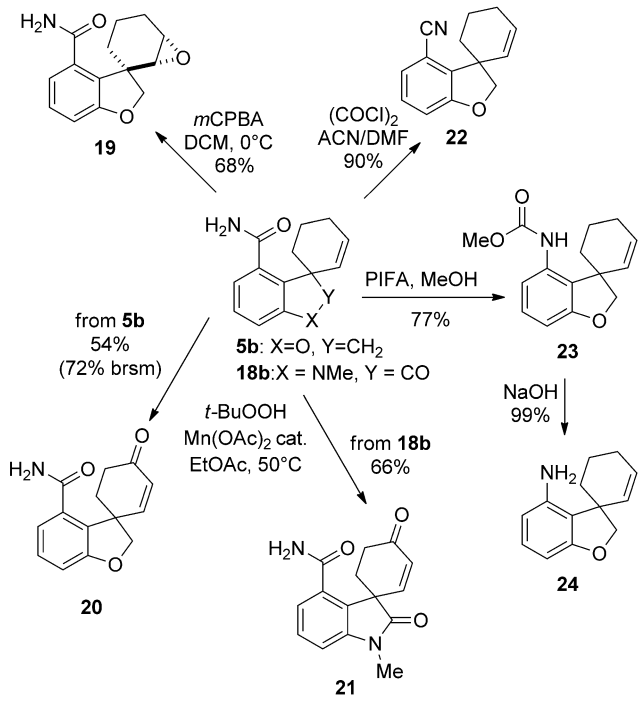
Table 2. Rh(III)-catalyzed Heck-type spirocyclization of benzamides **6a**–**18a**.



6a–18a **6b–18b**

Entry	Substrates	Products[a]	Entry	Substrates	Products[a]
1	 **6a**	 **6b** 88%	8	 **13a**	 **13b** 77%
2	 **7a**	 **7b** 72%	9	 **14a**	 **14b** 84%
3	 **8a**	 **8b** 79%	10	 **15a**	 **15b** 73%
4	 **9a**	 **9b** 70%	11	 **16a**	 **16b**, R = H, 23% **16c**, R = OMe, 10%
5	 **10a**	 **10b** 83%	12	 **16a**	 **16b** 57%[c]
6	 **11a**	 **11b** 76%	13	 **17a**	 **17b** 77%
7	 **12a**	 **12b** 60%[b]	14	 **18a**	 **18b** 60%[d]

[a] Isolated yield.
[b] Reaction carried out at 100 °C for 3 days, Yield brsm 69%.
[c] $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.1 equiv.) and $AgSbF_6$ (10 mol%) were used.
[d] 5 mol% of $[RhCp^*Cl_2]_2$ were used.



Scheme 2. Examples of the functionalization of spirocyclic compounds **5b** and **18b**.

forms well with the amide **18a** to give the spirooxindole building block **18b** in 60% yield (entry 14).

Having established the efficiency of the Rh(III)-catalyzed spirocyclization of benzamides **5a**–**18a**, we next explored some functionalizations (Scheme 2). We showed that from a single compound, a variety of *o*-substituted spirocycles could be obtained. For instance, epoxidation of the olefin of **5b**, using *m*CPBA, selectively afforded **19** in 68% yield. Manganese-catalyzed allylic oxidation of alkene **5b** gave the α,β-unsaturated ketone **20** in 54% yield (72% brsm). The same reaction performed on the spirooxindole **18b** led to the enone **21** in 66% yield.

The utility of the primary benzamide resulting from the cyclization was next illustrated. Its efficient transformation into a nitrile group was achieved by using oxalyl chloride (i.e., **22**, 90%). Furthermore, hypervalent iodine-mediated Hofmann rearrangement in methanol afforded methyl carbamate **23** in 77% yield. In turn, hydrolysis of compound **23** furnished quantitatively the spirocyclic aniline **24**.

In summary, we have developed a practical and straightforward synthesis of sterically hindered *ortho*-substituted aryl spirocycles using a Rh(III)-catalyzed ArCH activation/intramolecular Heck-type reaction. This approach is tolerant with electron withdrawing and donating groups on the aromatic ring, and allows the synthesis of [6,5,6], [6,5,5], [6,5,7], and [6,6,6] aryl spirocyclic systems. Some of these compounds were converted into diversely substituted spiro-linked heterocycles that could be of interest in medicinal chemistry or in the total synthesis of natural products.

Experimental Section

General Procedure; Ether Synthesis by Mitsunobu Reaction

To a solution of phenol (1 equiv.), allylic alcohol (1 equiv.), triphenylphosphine (1.4 equiv.) in THF (5 mL mmol^{-1}) was added diethyl azodicarboxylate (1.4 equiv.) at 0 °C. The reaction mixture was stirred overnight at room temperature. Then the reaction mixture was diluted with EtOAc and the organic layer was washed with water followed by brine. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture purified through silica gel to afford the corresponding ether.

General Procedure; Acid Synthesis

To a solution of ester (1 equiv.) in ethanol (5.9 mL mmol^{-1}) was added a 3 M solution of NaOH (3.5 mL mmol^{-1}) at room temperature. The mixture was stirred for 2 h, then HCl (2 N) was added at 0 °C until pH 2–3. The aqueous layer was extracted with EtOAc and the solvent was evaporated under vacuum. The crude mixture was used without purification.

General Procedure; Amide Synthesis

The corresponding carboxylic acid (1 equiv.) was dissolved in dichloromethane (5 mL mmol^{-1}) and oxalyl chloride (1.2 equiv) was added. One drop of DMF was added and the solution was stirred at room temperature for 30 min. The mixture was concentrated by rotavap. Ethyl acetate (2.7 mL mmol^{-1}), *O*-methylhydroxylamine hydrochloride (1.1 equiv.), potassium carbonate (2.4 equiv), and water (1.3 mL mmol^{-1}) were added in succession, and the suspension was stirred for five hours. The aqueous layer was separated and extracted once with ethyl acetate. The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The solvent was removed under vacuum and the crude mixture purified through silica gel to afford the corresponding amide.

General Procedure; Rhodium(III)-Catalyzed Heck-Type Reaction

A sealed tube was charged with a stir bar, amide (1 equiv.), $[RhCp^*Cl_2]_2$ (0.025 equiv.) and CsOAc (2 equiv.). The tube was purged three times by vacuum and argon, then MeOH (0.2 M) was added. The vial was sealed and the mixture stirred at the indicated temperature for the indicated time. The reaction mixture was concentrated under vacuum. The crude residue was purified by column chromatography on silica gel to afford the corresponding spirocycle.

Acknowledgements

This work was supported by CNRS and ICSN.

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